alternative spliced exons	no. of amino acids encoded
α	21
β	37
γ	38

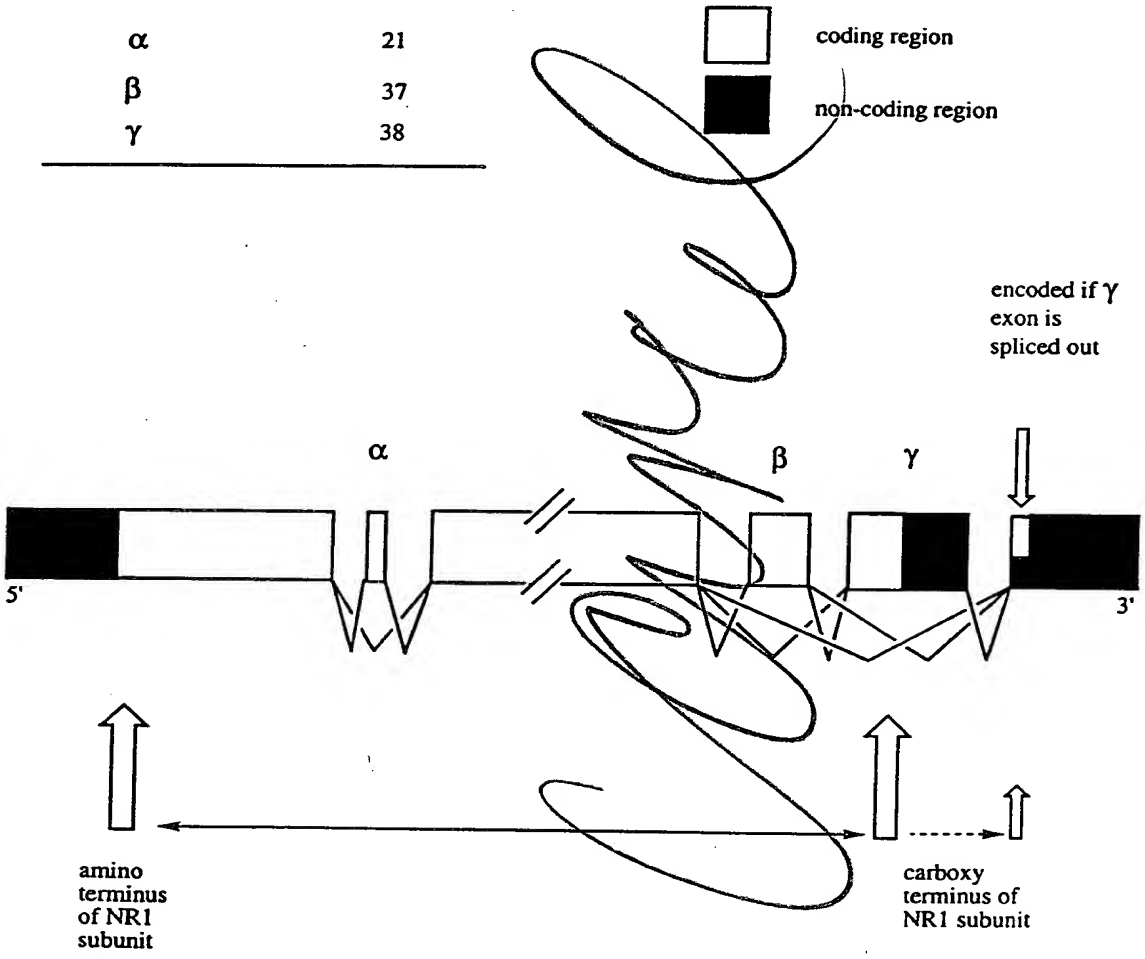


FIG. 1

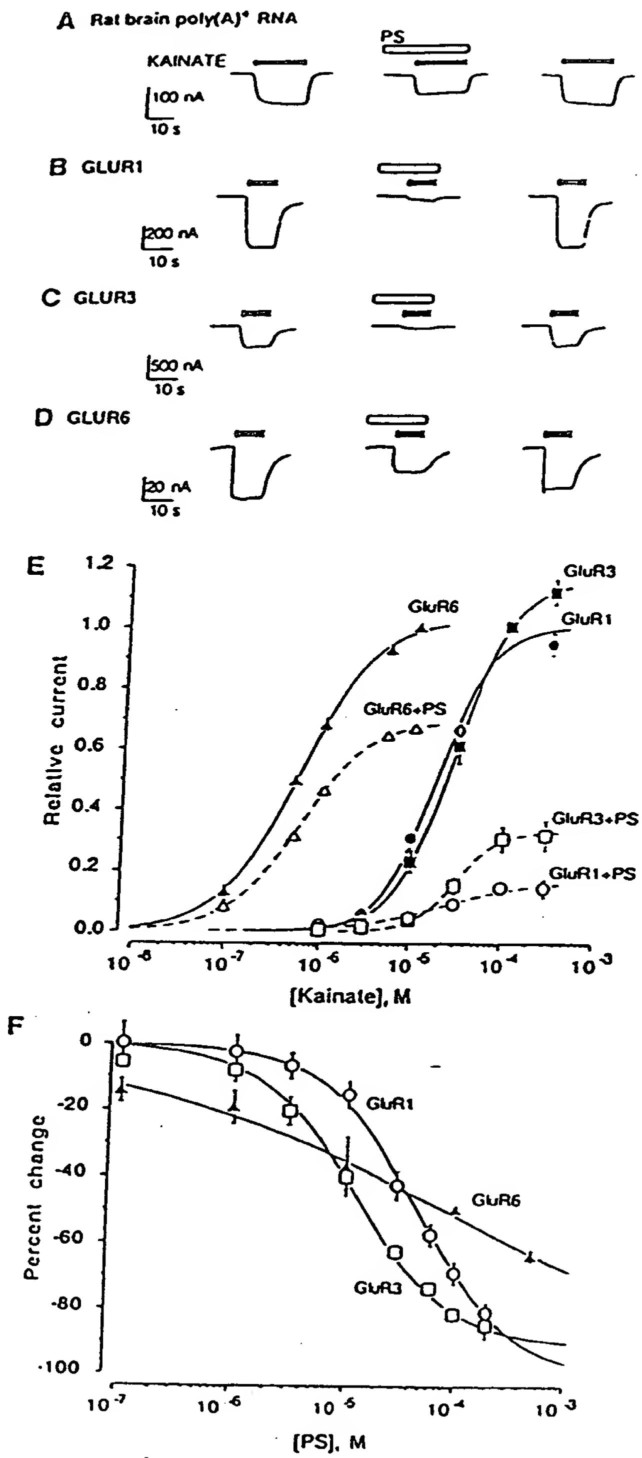


FIG. 2

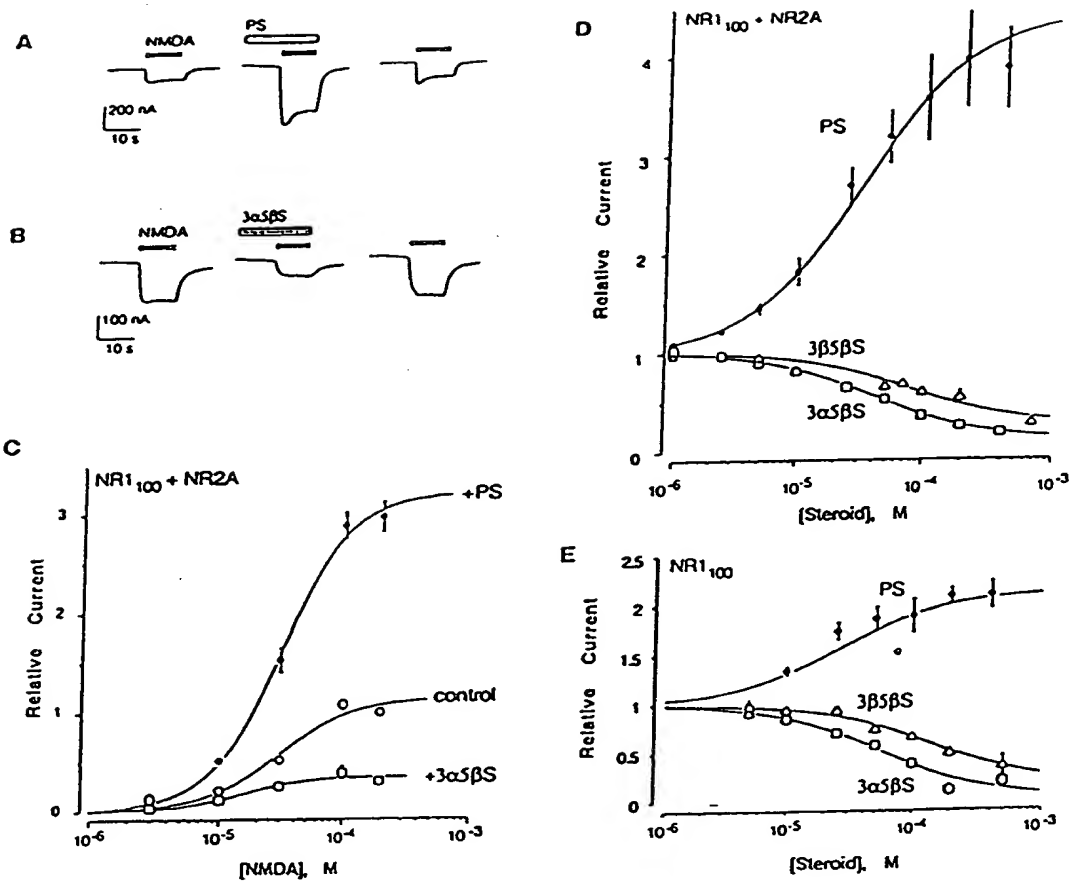

A
NMDA
PS
200 nA
10 s
B
NMDA
3αSβS
100 nA
10 s
C
NR1100 + NR2A
+PS
control
+3αSβS
Relative Current
[NMDA], M
D
NR1100 + NR2A
PS
3βSβS
3αSβS
Relative Current
[Steroid], M
E
NR1100
PS
3βSβS
3αSβS
Relative Current
[Steroid], M

FIG. 3

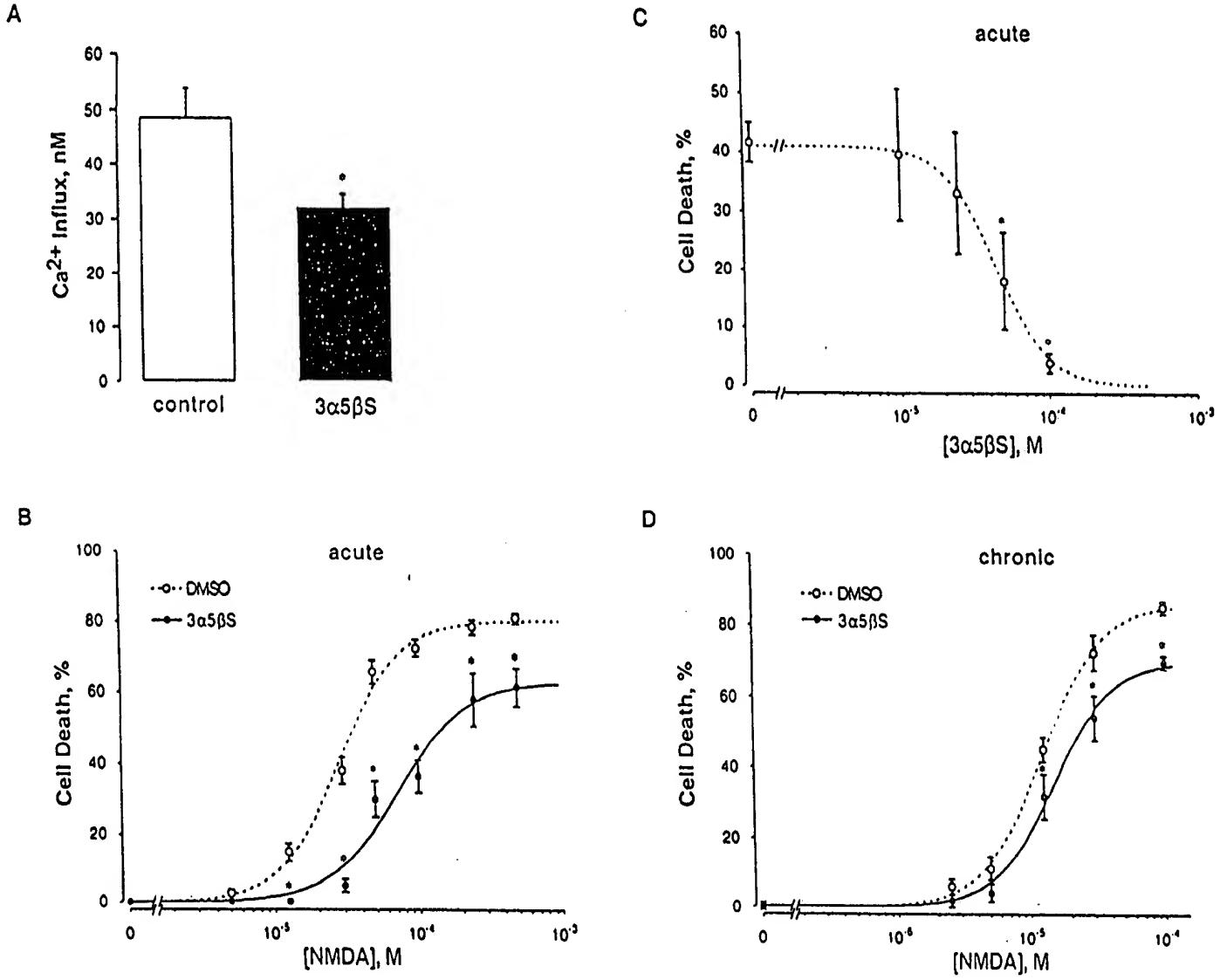

A
Ca^{2+} Influx, nM
60
50
40
30
20
10
0
control
3α5βS
C
acute
Cell Death, %
60
50
40
30
20
10
0
0
10^{-5}
10^{-4}
10^{-3}
[3α5βS], M
B
acute
DMSO
3α5βS
Cell Death, %
100
80
60
40
20
0
0
10^{-5}
10^{-4}
10^{-3}
[NMDA], M
D
chronic
DMSO
3α5βS
Cell Death, %
100
80
60
40
20
0
0
10^{-6}
10^{-5}
10^{-4}
[NMDA], M

FIG. 4

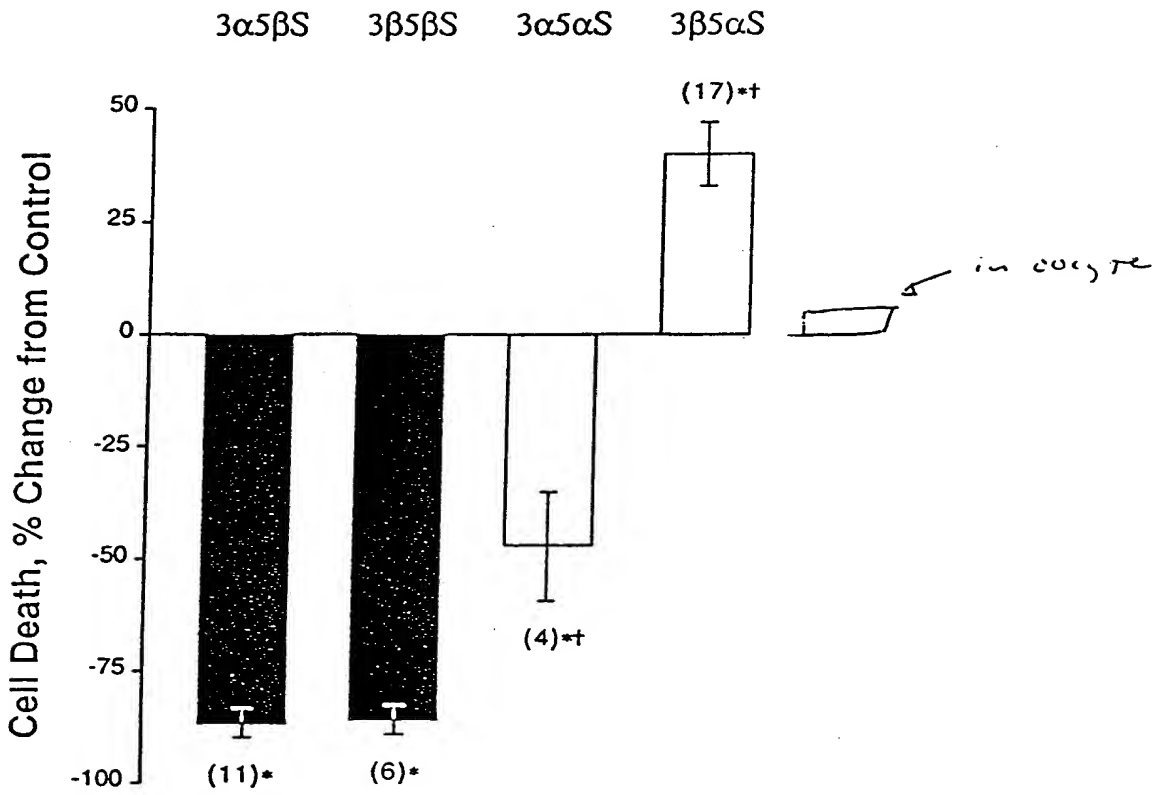

3α5βS
3β5βS
3α5αS
3β5αS
(17)*†
50
25
0
-25
-50
-75
-100
Cell Death, % Change from Control
(11)*
(6)*
(4)*†
in oocyte

FIG. 5

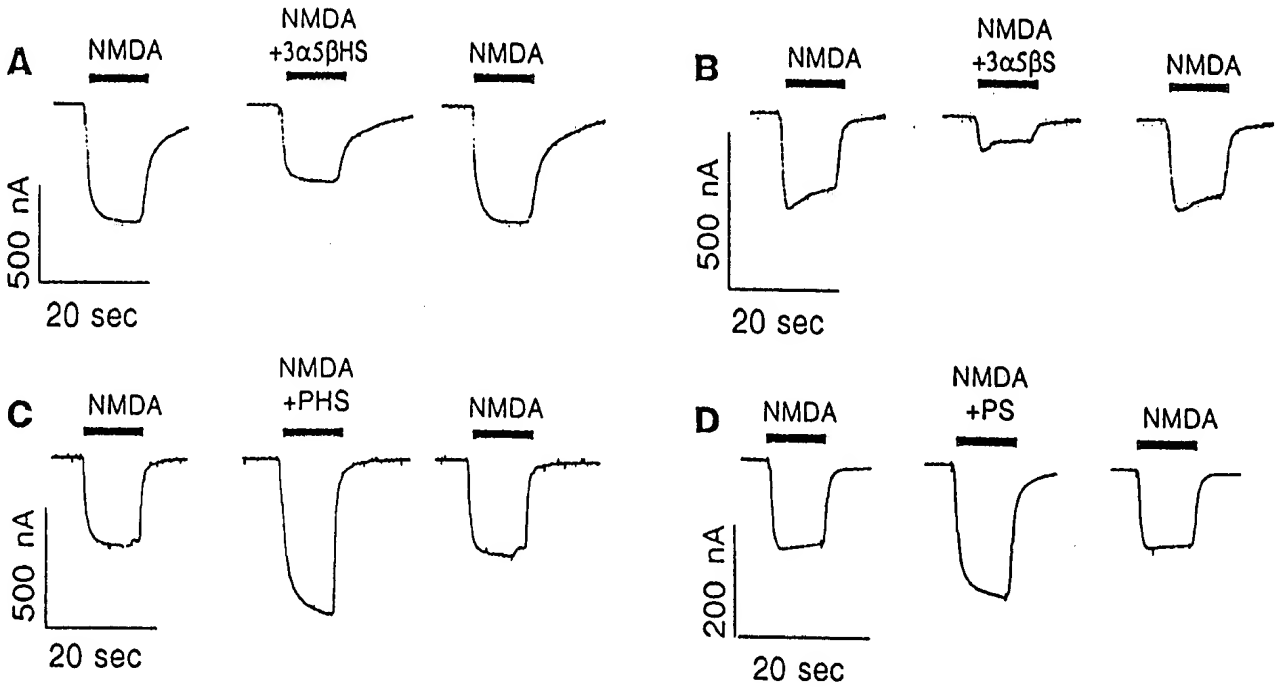


FIG. 6

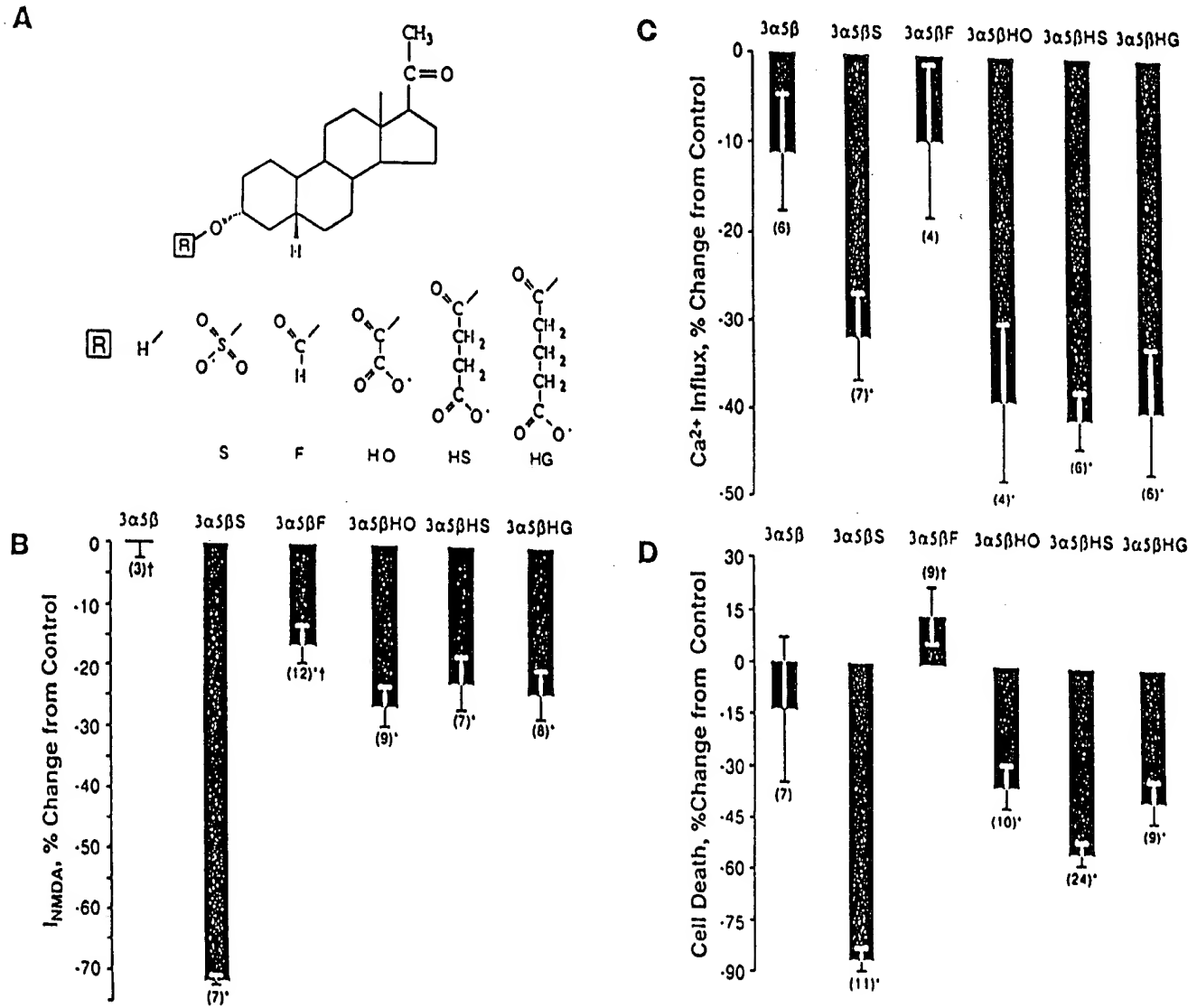

A
R
H
S
F
HO
HS
HG
B
I_{NMDA}, % Change from Control
3α5β
3α5βS
3α5βF
3α5βHO
3α5βHS
3α5βHG
(3)†
(7)*
(12)*†
(9)*
(7)*
(8)*
C
Ca^{2+} Influx, % Change from Control
(6)
(7)*
(4)
(4)*
(6)*
(6)*
D
Cell Death, %Change from Control
(7)
(11)*
(9)†
(10)*
(24)*
(9)*

FIG. 7

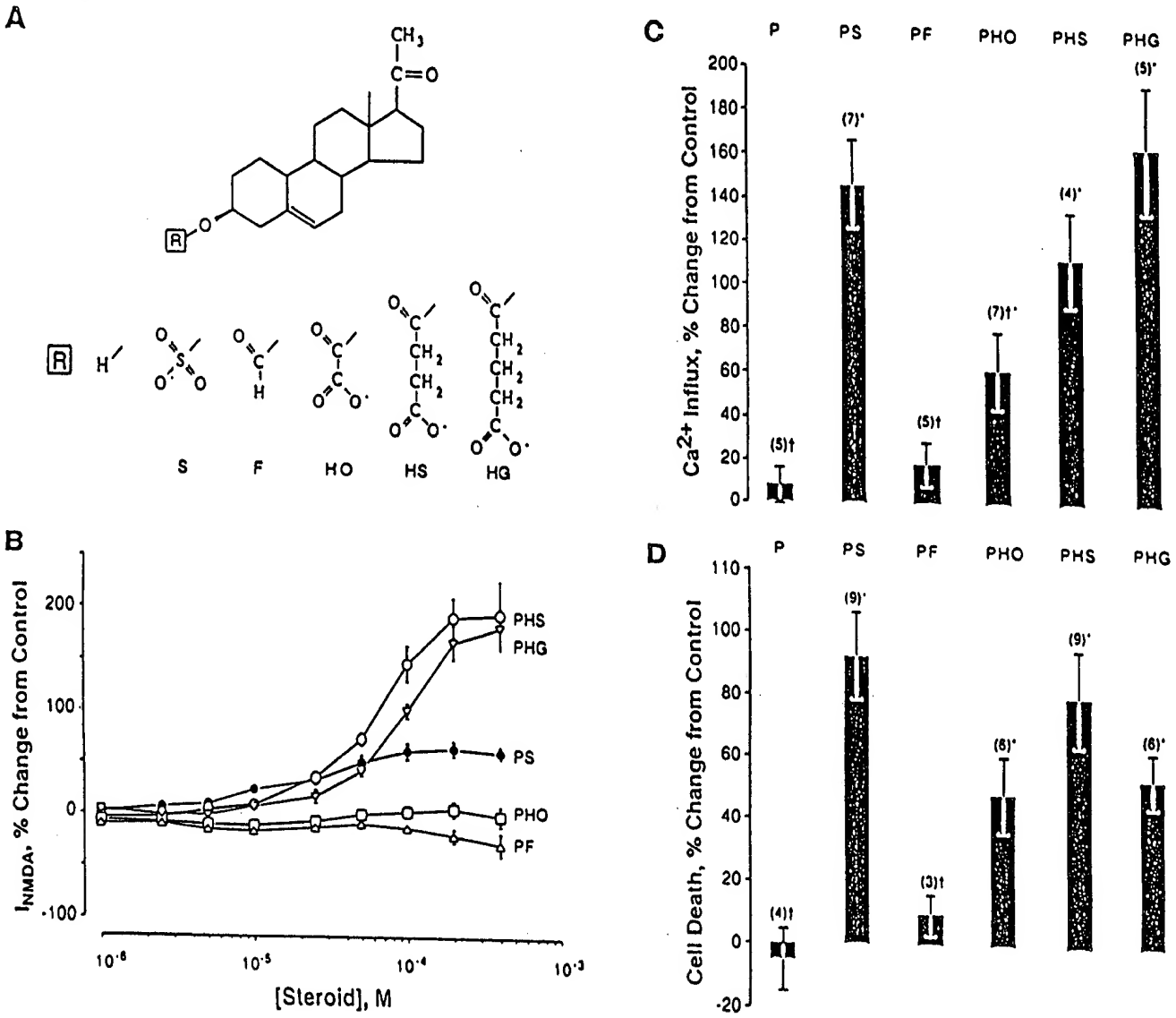


FIG. 8

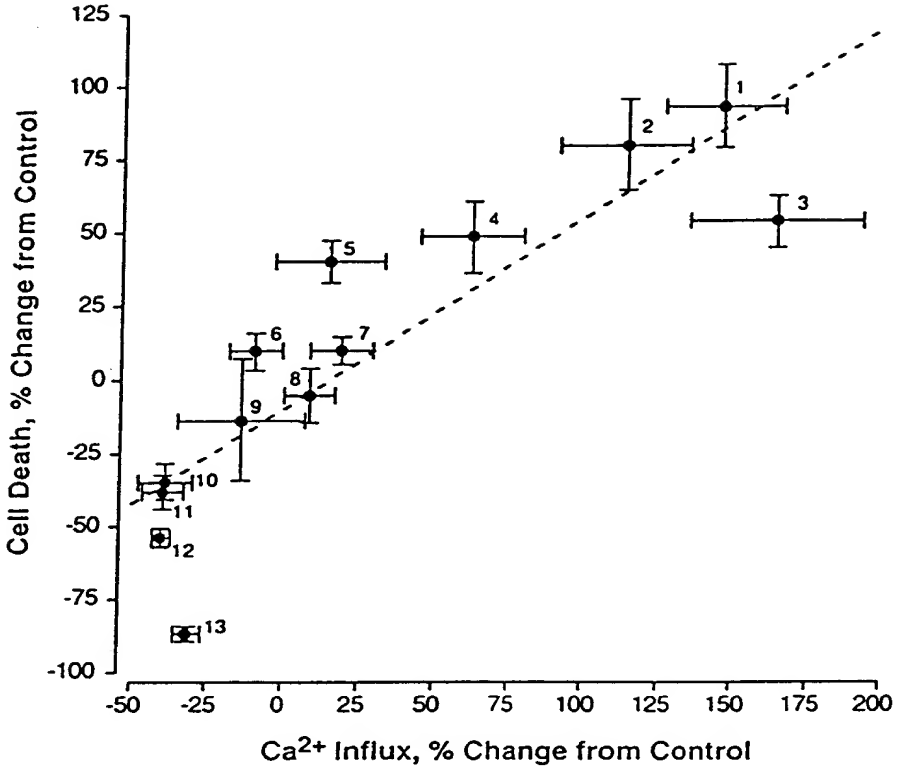
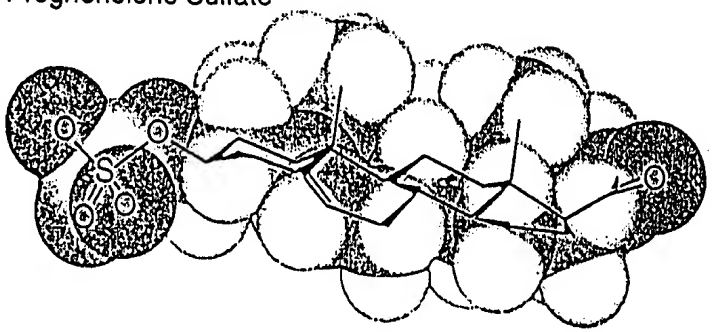


FIG. 9

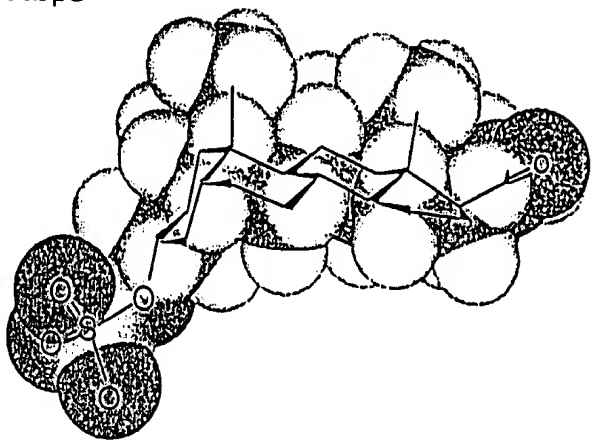
Positive Modulators

Pregnenolone Sulfate

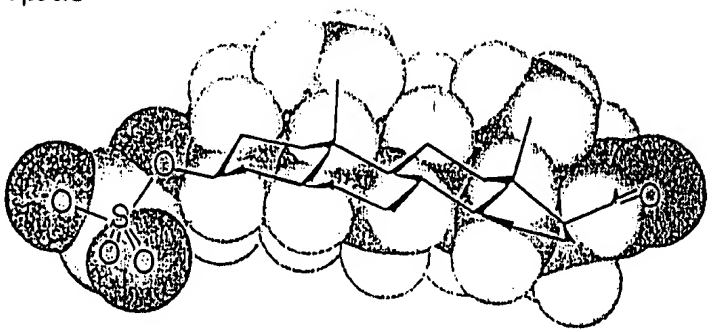


Negative Modulators

3α5βS



3β5αS



3β5βS

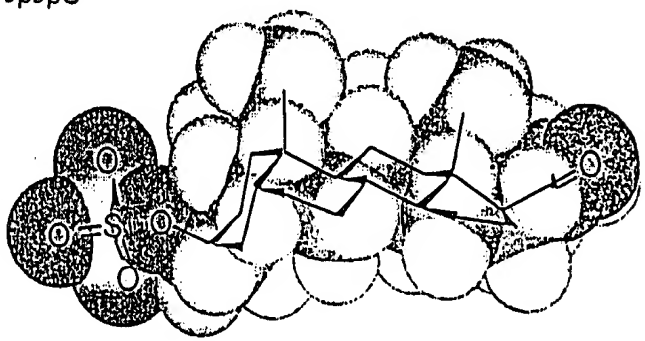


FIG. 10

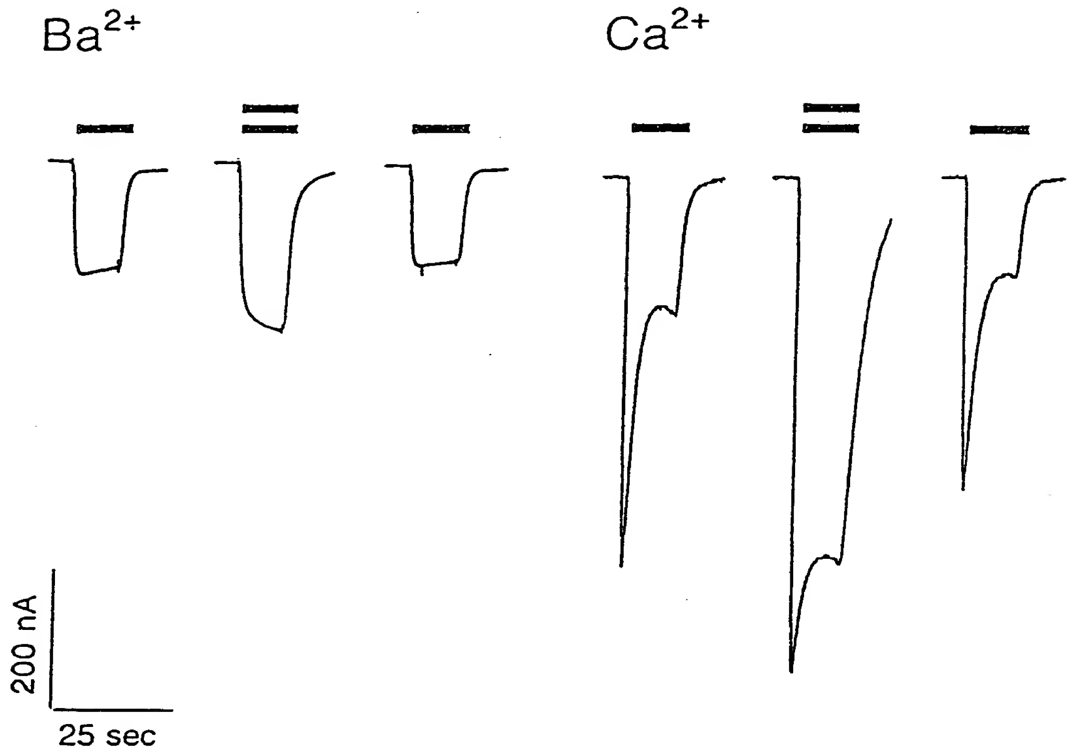
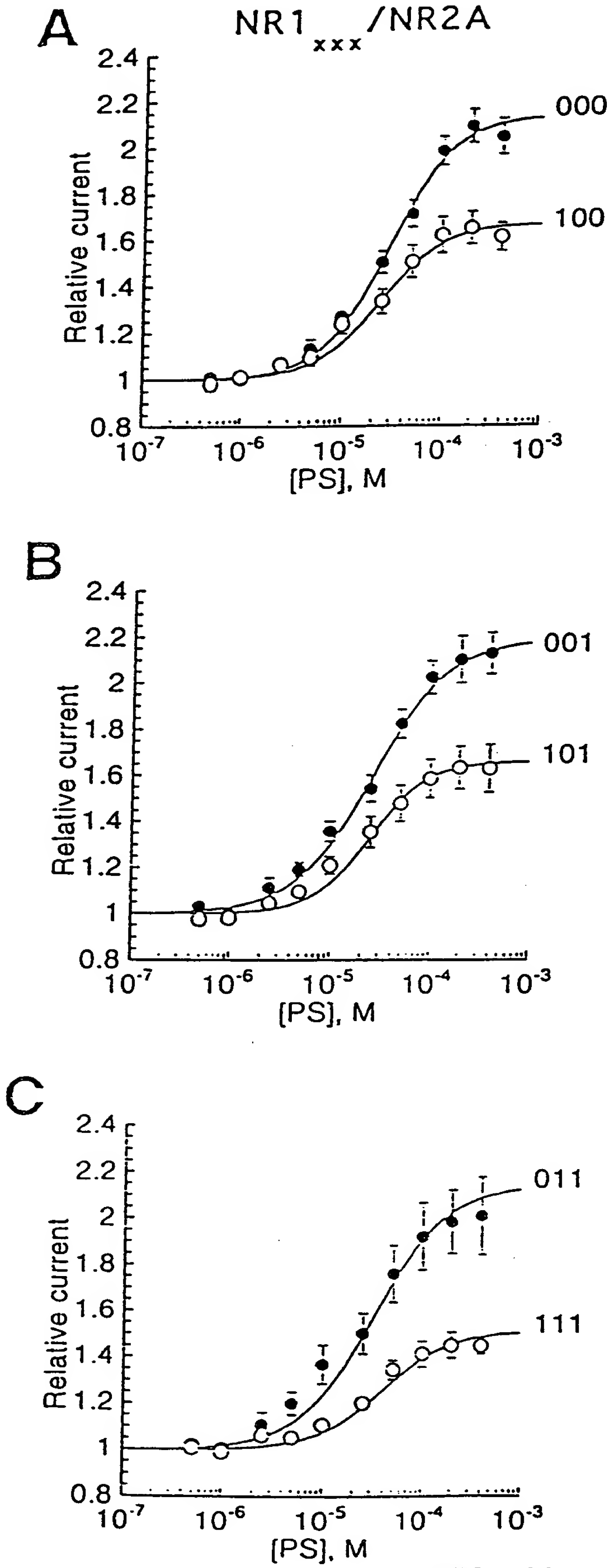


FIG. 11



NR1G/NR2A
NR1E/NR2A

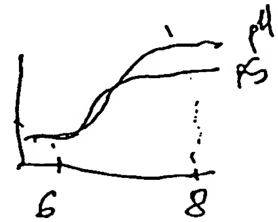


FIG. 12

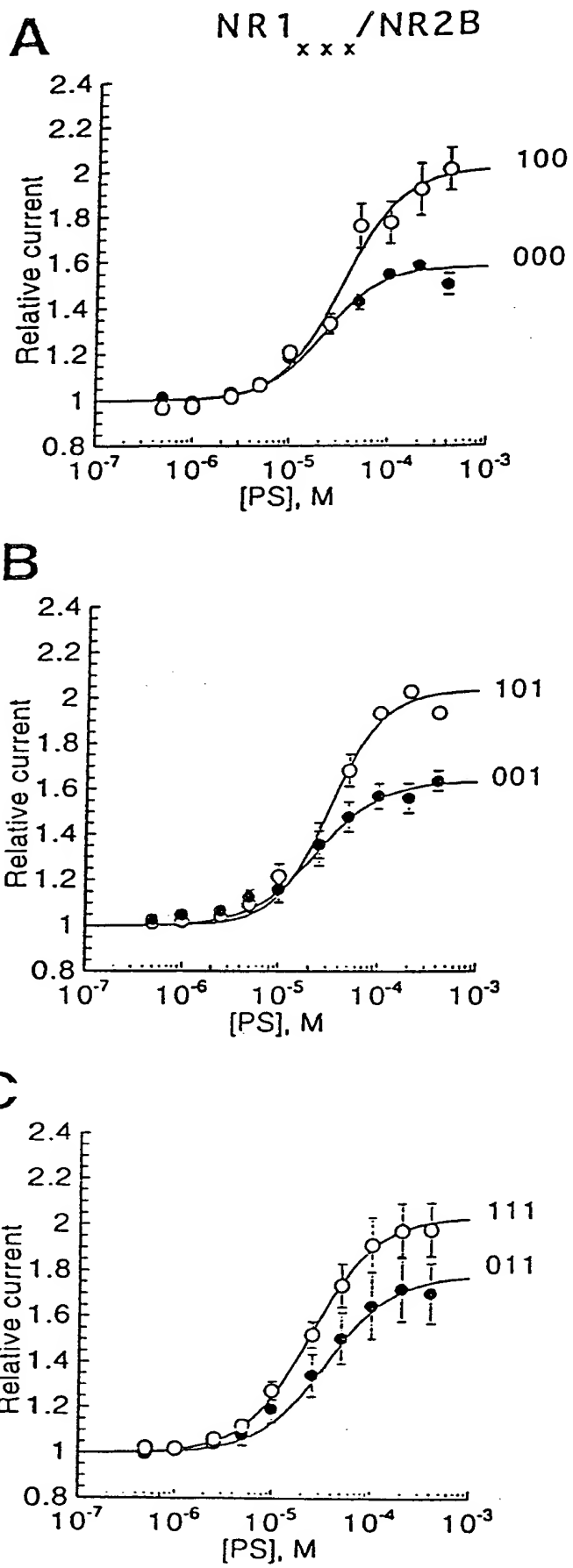
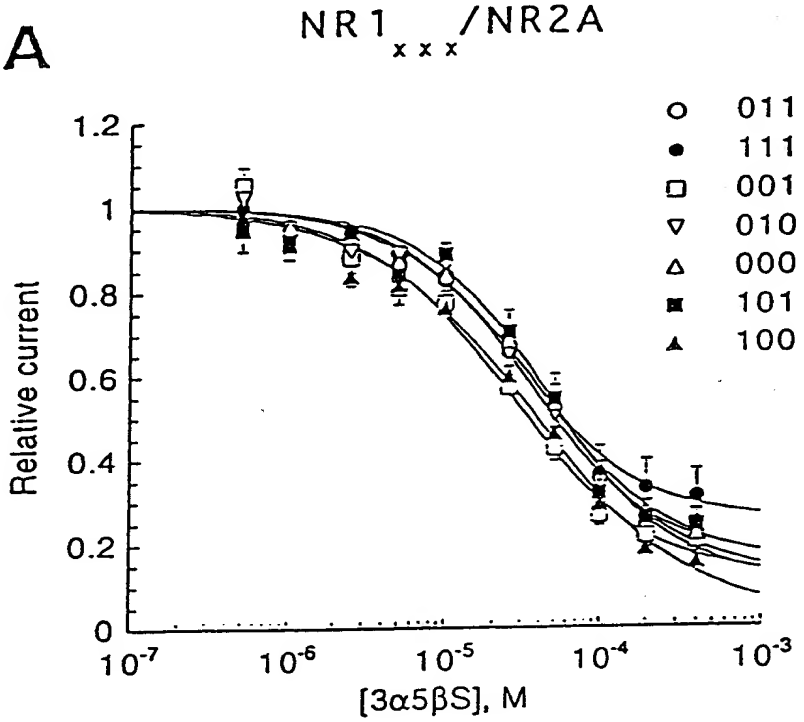


FIG. 13


A
NR1xxx/NR2A
011
111
001
010
000
101
100
Relative current
1.2
1
0.8
0.6
0.4
0.2
0
10-7
10-6
10-5
10-4
10-3
[3α5βS], M

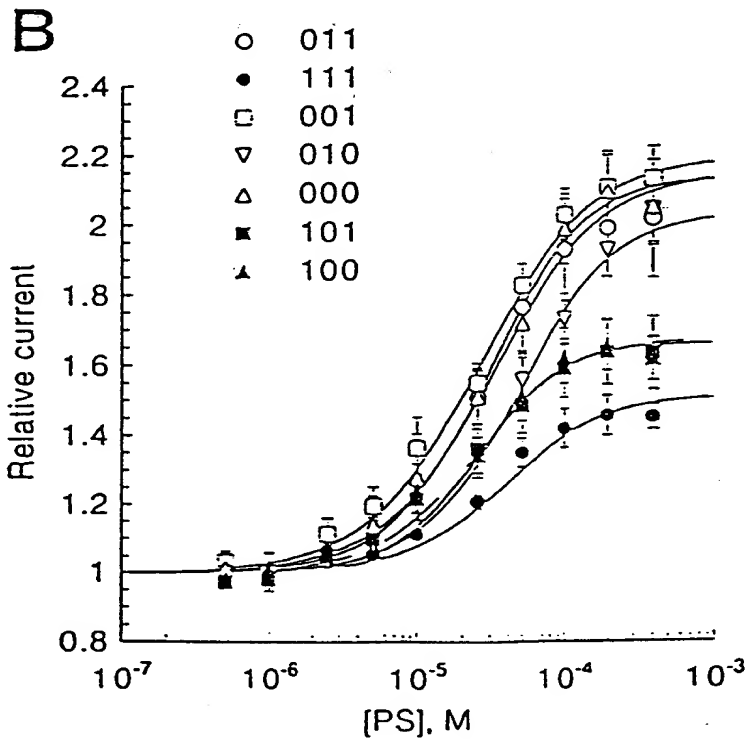

B
011
111
001
010
000
101
100
Relative current
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
10-7
10-6
10-5
10-4
10-3
[PS], M

FIG. 14

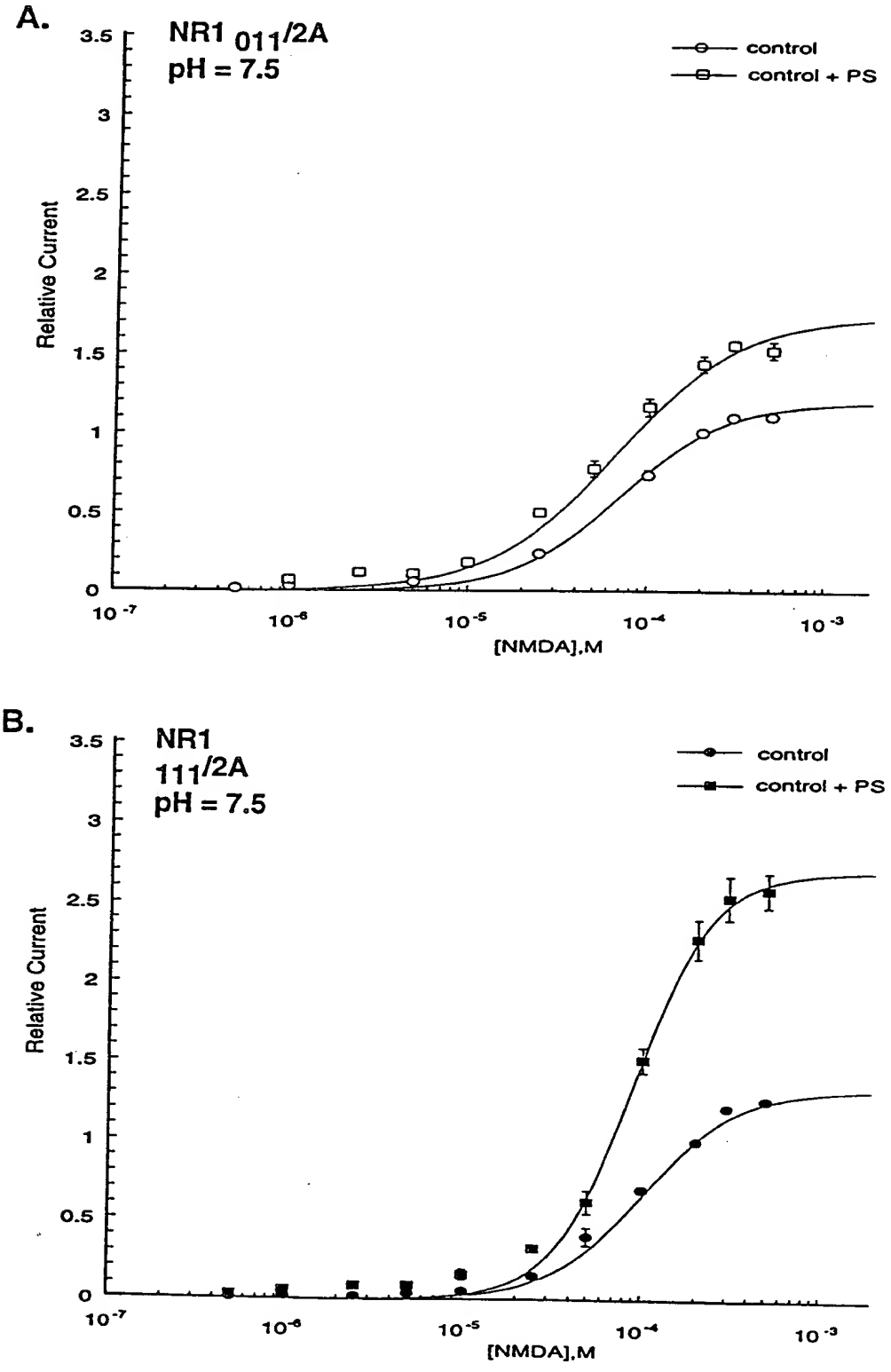

A.
NR1 011/2A
pH = 7.5
control
control + PS
Relative Current
3.5
3
2.5
2
1.5
1
0.5
0
10 -7
10-6
10-5
10-4
10 -3
[NMDA],M
B.
NR1
111/2A
pH = 7.5
control
control + PS
Relative Current
3.5
3
2.5
2
1.5
1
0.5
0
10-7
10-6
10-5
10-4
10-3
[NMDA],M

FIG. 15

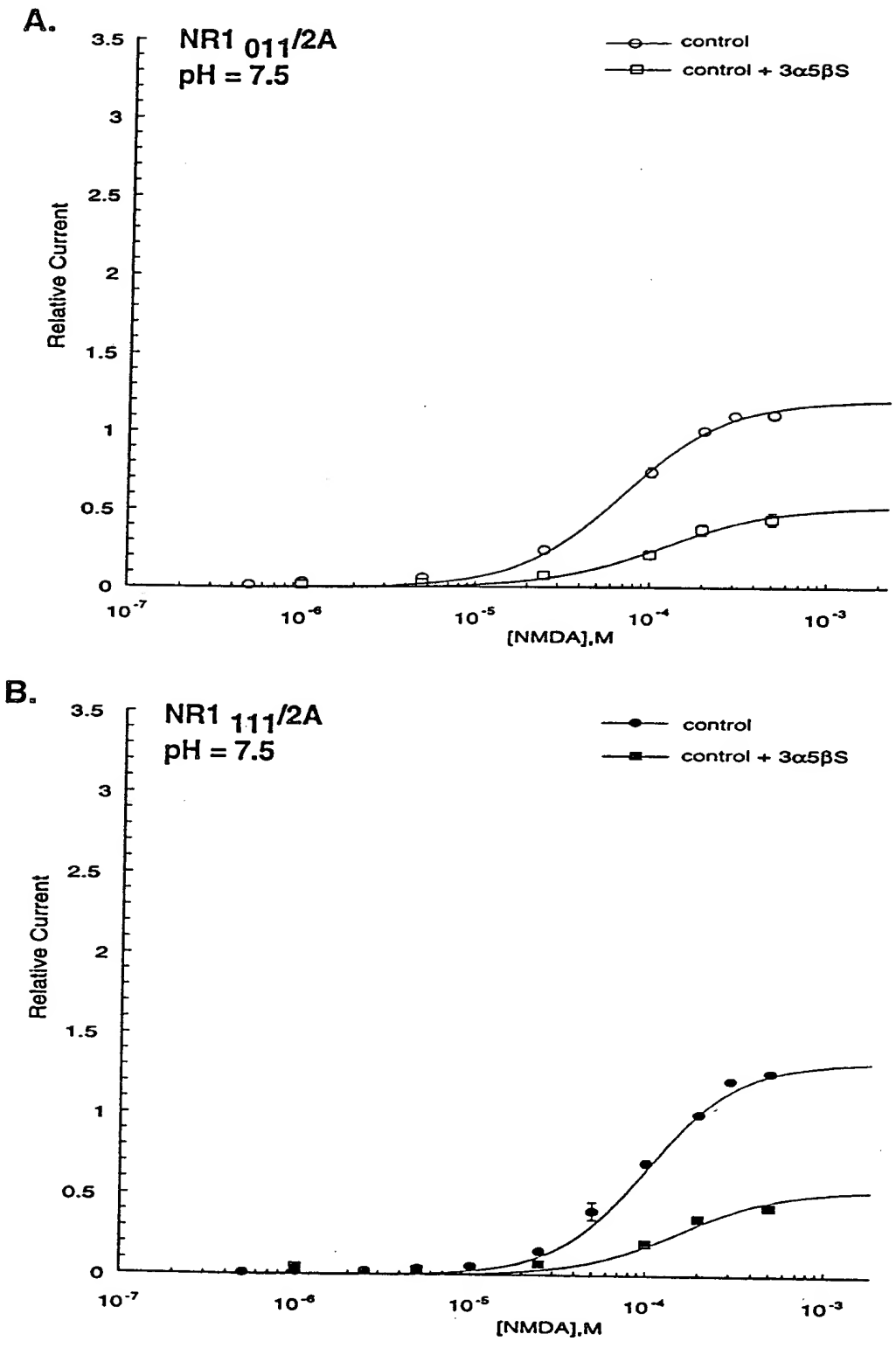
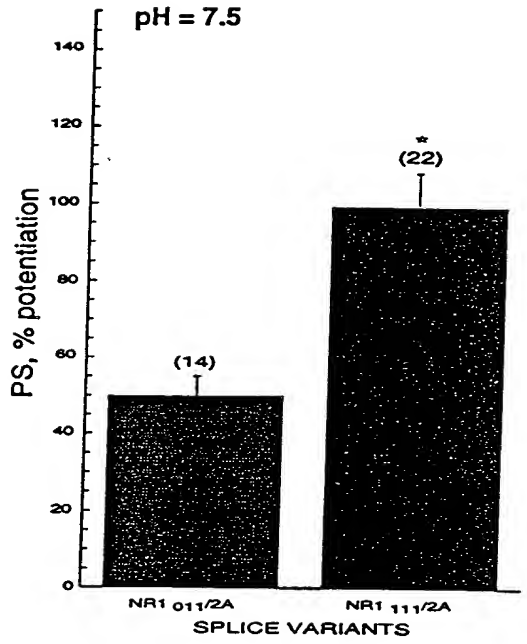

A.
NR1 011/2A
pH = 7.5
control
control + 3α5βS
Relative Current
3.5
3
2.5
2
1.5
1
0.5
0
10-7
10-6
10-5
10-4
10-3
[NMDA],M
B.
NR1 111/2A
pH = 7.5
control
control + 3α5βS
Relative Current
3.5
3
2.5
2
1.5
1
0.5
0
10-7
10-6
10-5
10-4
10-3
[NMDA],M

FIG. 16

A.


pH = 7.5
PS, % potentiation
140
120
100
80
60
40
20
0
(14)
(22)
*
NR1 011/2A
NR1 111/2A
SPLICE VARIANTS

B.

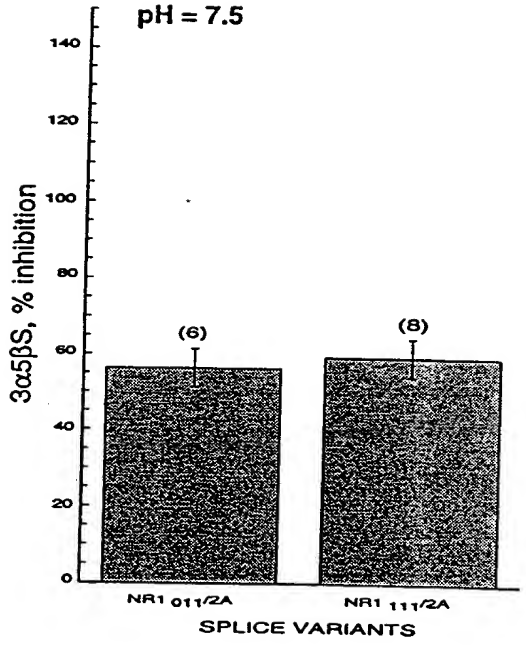

pH = 7.5
3α5βS, % inhibition
140
120
100
80
60
40
20
0
(6)
(8)
NR1 011/2A
NR1 111/2A
SPLICE VARIANTS

FIG. 17

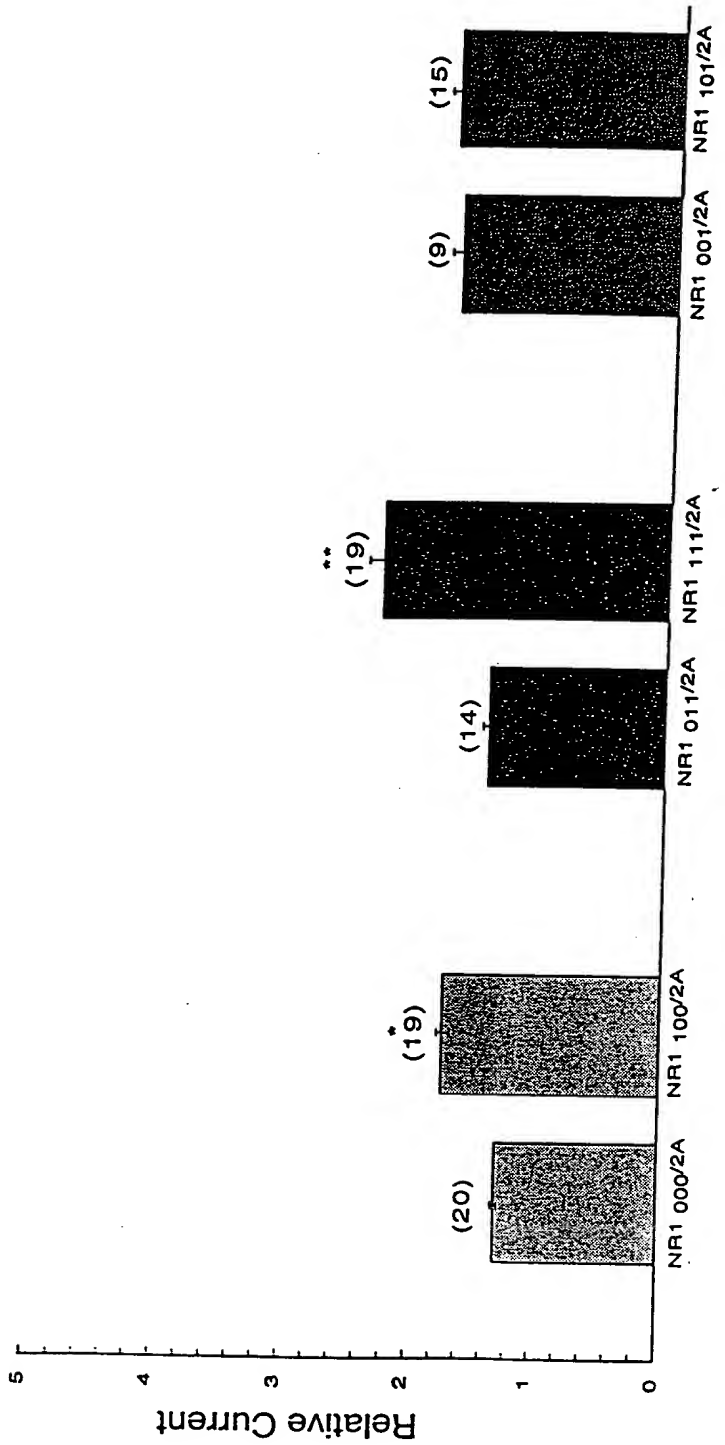


FIG. 18

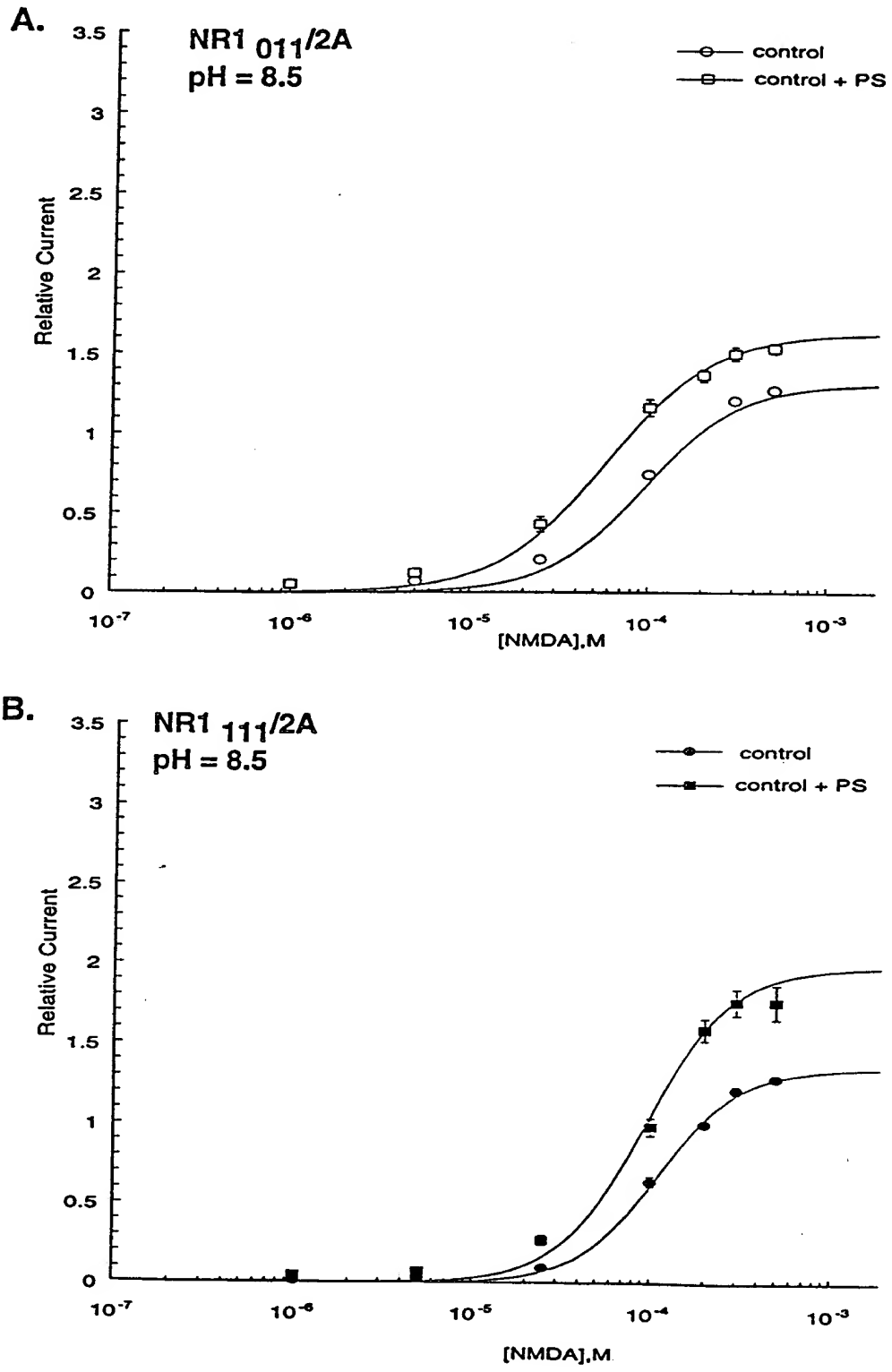

A.
NR1 011/2A
pH = 8.5
control
control + PS
Relative Current
3.5
3
2.5
2
1.5
1
0.5
0
10-7
10-6
10-5
10-4
10-3
[NMDA],M
B.
NR1 111/2A
pH = 8.5
control
control + PS
Relative Current
3.5
3
2.5
2
1.5
1
0.5
0
10-7
10-6
10-5
10-4
10-3
[NMDA],M

FIG. 19

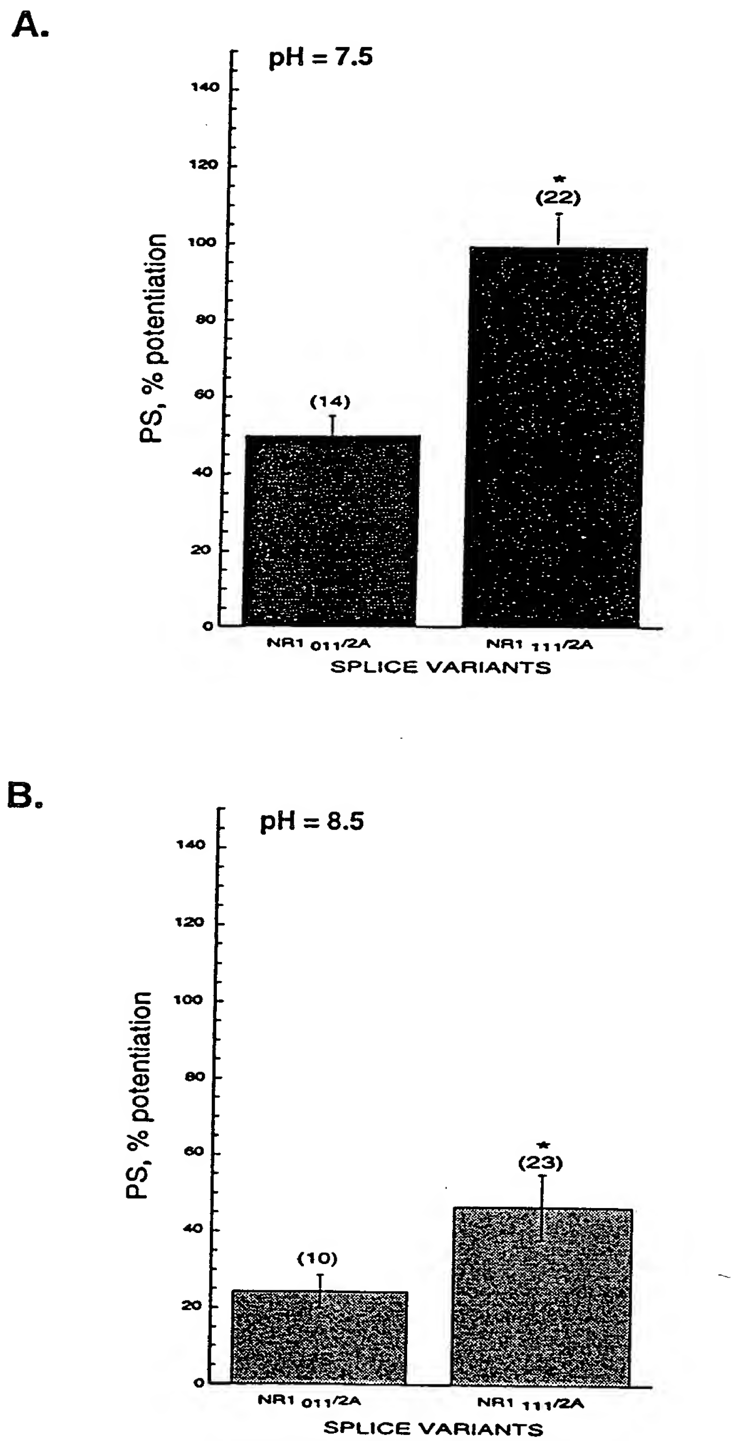

A.
pH = 7.5
PS, % potentiation
140
120
100
80
60
40
20
0
(14)
*
(22)
NR1 011/2A
NR1 111/2A
SPLICE VARIANTS
B.
pH = 8.5
PS, % potentiation
140
120
100
80
60
40
20
0
(10)
*
(23)
NR1 011/2A
NR1 111/2A
SPLICE VARIANTS

FIG. 20

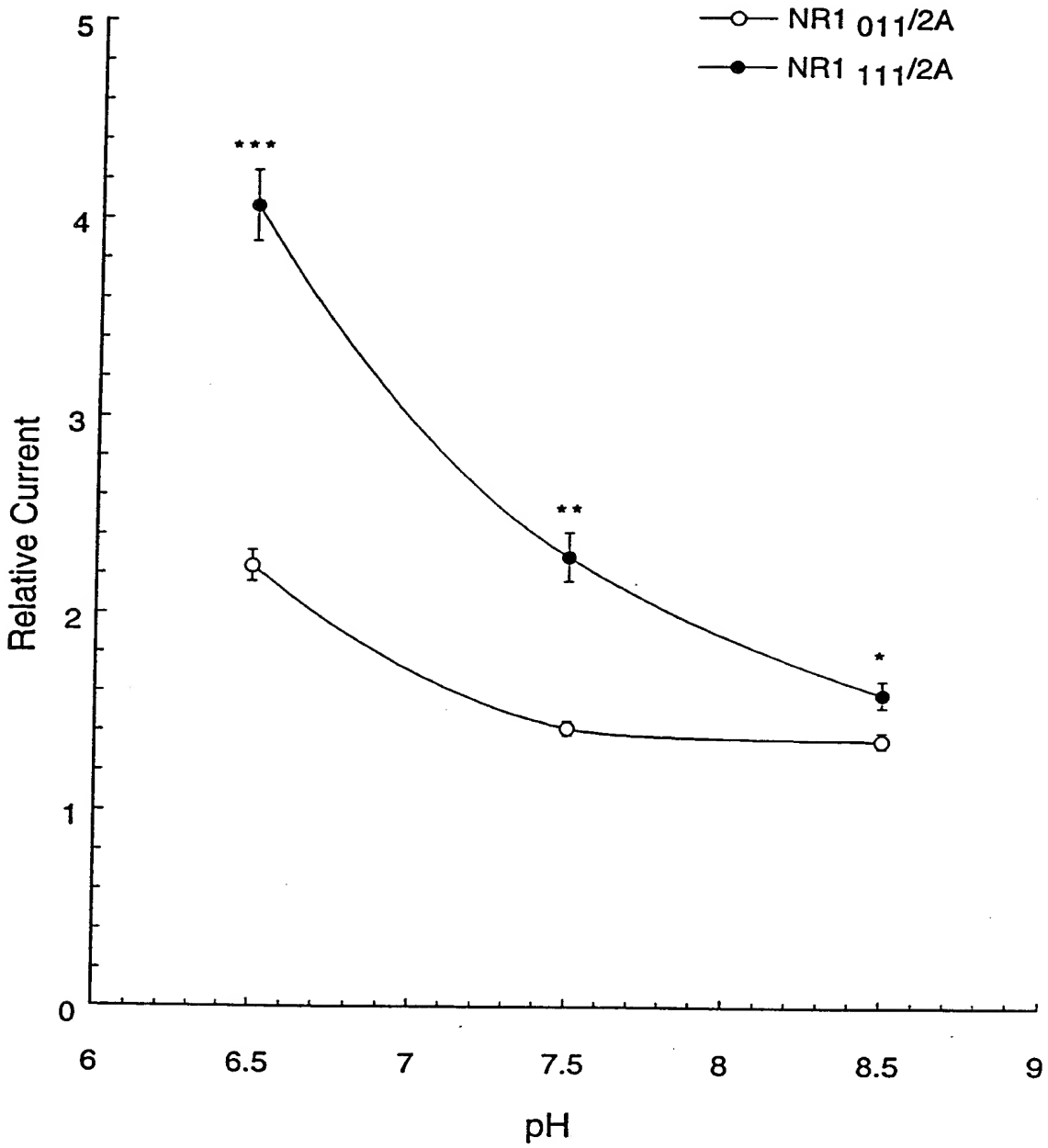


FIG. 21

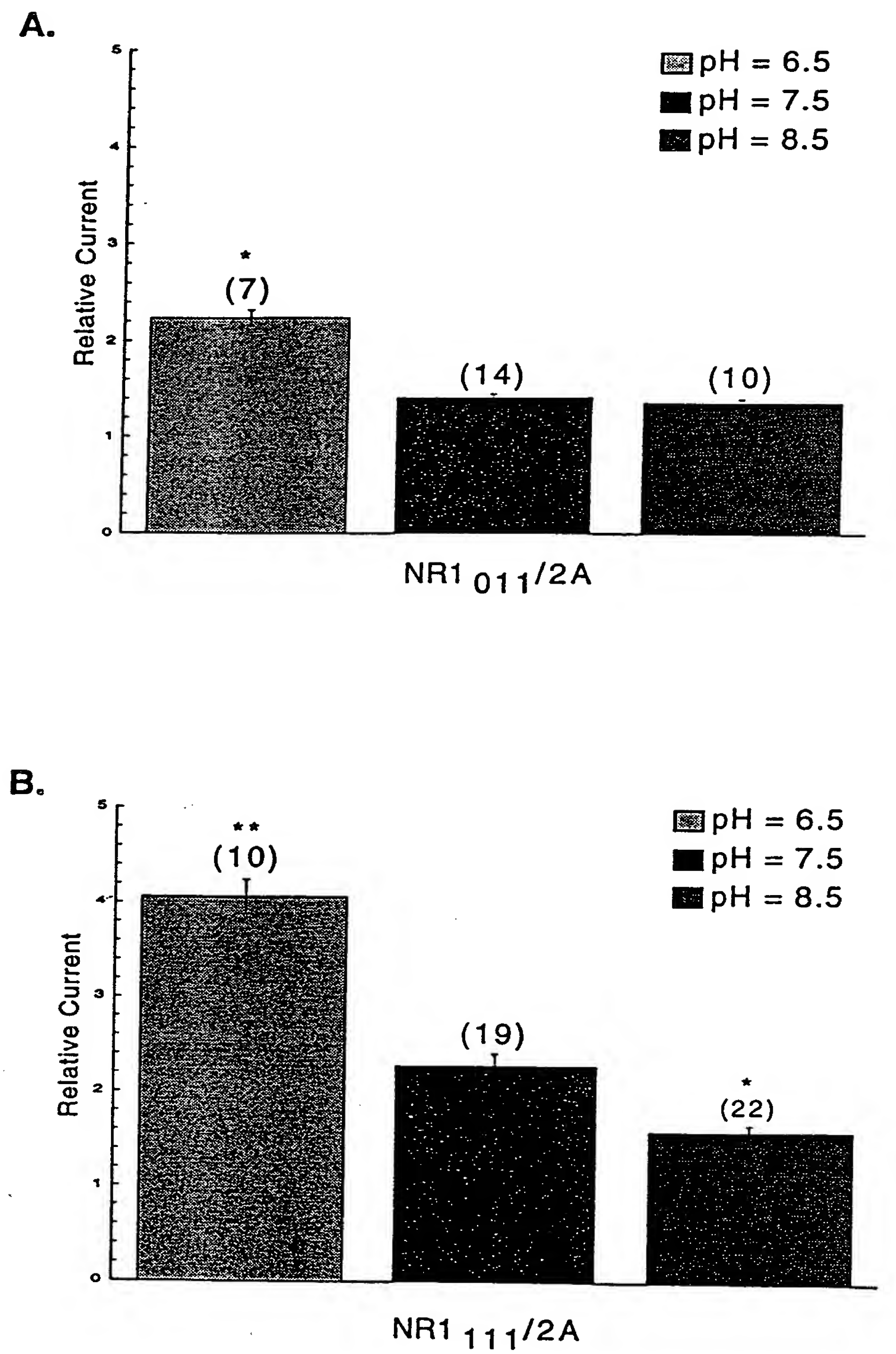


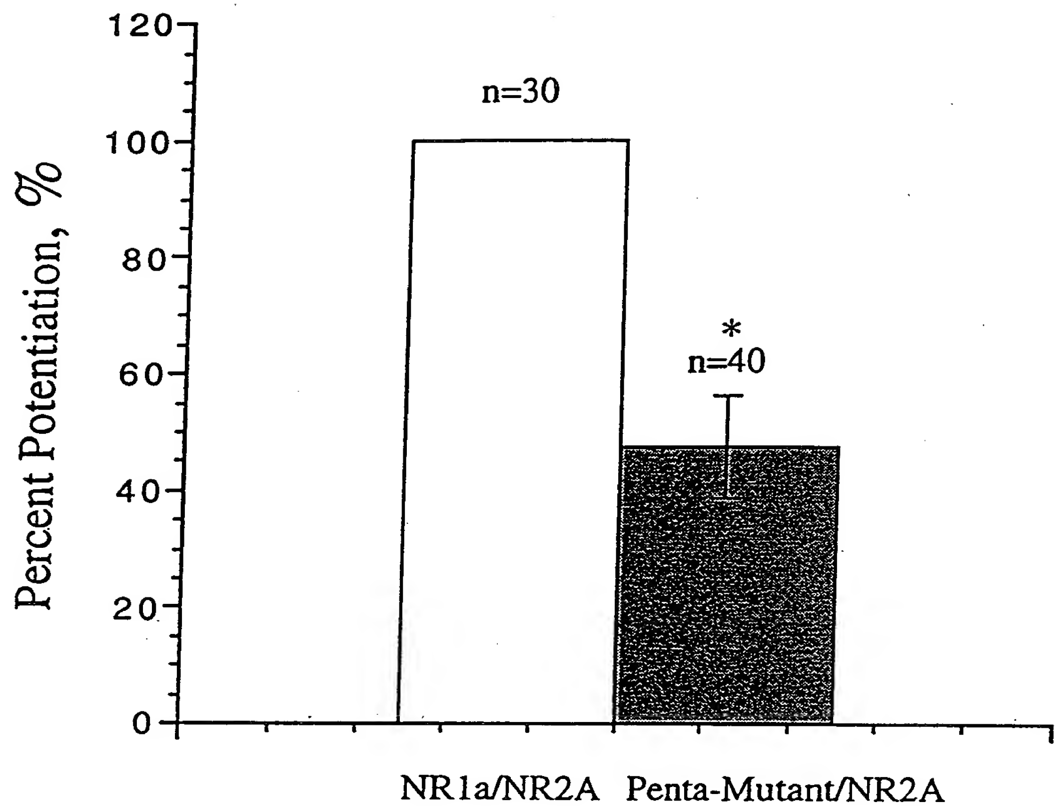
FIG. 22

```
RXR-α     ILE.AELAVEPKTETYVEANMGL.NPSSPNDPVTNIC.QAADKQLFTL
RAR       LCQLGKYTTNSSADHRVQLDLGLWDKFS..ELATK.C..II.K....I
PR        IN.LLM.SIEPDV.IYAGHD.N.TKPDTSSSLLTSL.NQLGERQLLSV
GCR       VS.LLE.VIEPEV.LYAGYD.S.SVPDSTWRIMTTL.NMLGGRQVIAA
ER         SALLD.A.EPPI.LYSEYD.P.TRPFSEASMMGLLTN.LADRELVHM
NR1011    IILLVSDDHEGRAA.QKRLETLLEERESKAEKVLQF.DP.GTKNVTAL   207
                                  Δ         Δ                Δ

RXR-α     V.EWAKRIPH.FSELPL..DDQVILLRAGWNELLIA..SFSHR.SIA
RAR       V.EFAKRLPG.FTGLSI..ADQITLLKAACLDILML..RICTR.YTP
PR        V.KWSKSLPG.FRNLHI..DDQITLIQYSWM.SLMV.FGLGWR.SYK
GCR       V.KWAKAIPG.FRNLHL..DDQMTLLQYSWM.FLMA.FALGWR.SYR
ER        I.NWAKRVPG.FVDLTL..HDQVHLLECAWLEILMI..GLVWR.SME
NR1011    LME.ARELEARVIILSASEDDAATVYRAAAM.LNMTGSGYVWLVGER    252
                                   Δ                        Δ

RXR-α     VKDG.IL.LATG.LH.VHR.N
RAR       EQDT.MT.FSDG.LT.LNR
PR        HVSGQMLYFAPD.LI.L...N
GCR       QSSANLLCFAPD.LI.I...N
ER        H.PGKLL.FAPN.LL.LDR.N
NR1011    EISGNALRYAPDGIIGLQLIN   273
```

FIG. 23



120
100
80
60
40
20
0
Percent Potentiation, %
n=30
*
n=40
NR1a/NR2A
Penta-Mutant/NR2A

FIG. 24

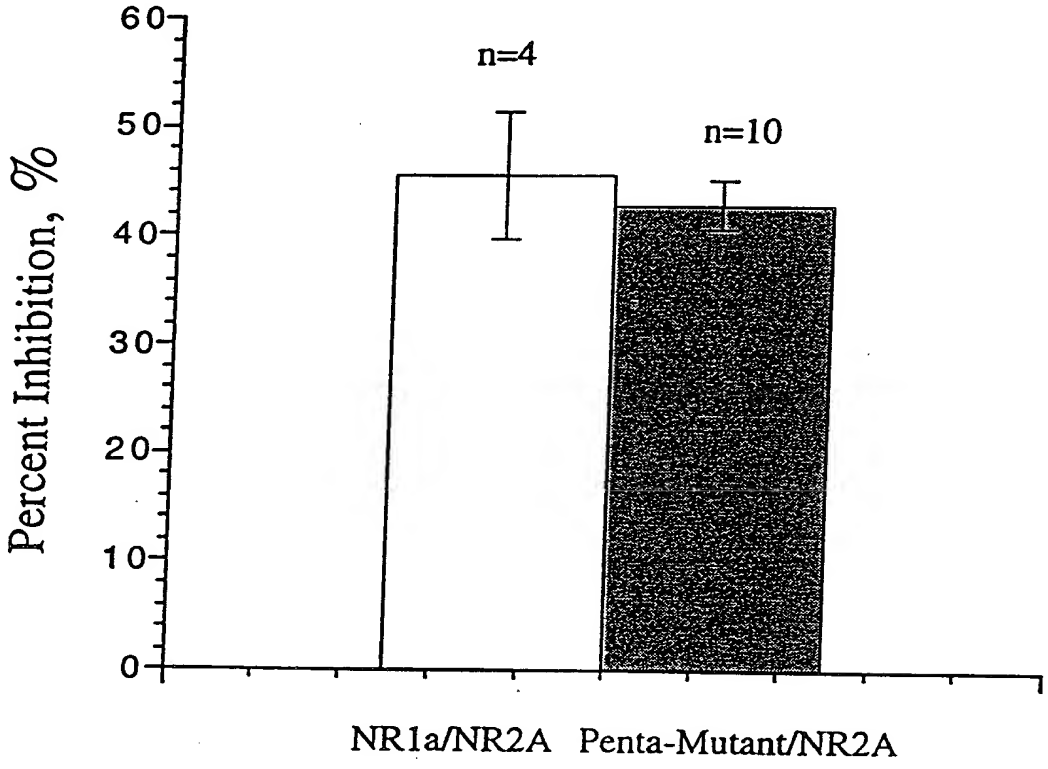


FIG. 25

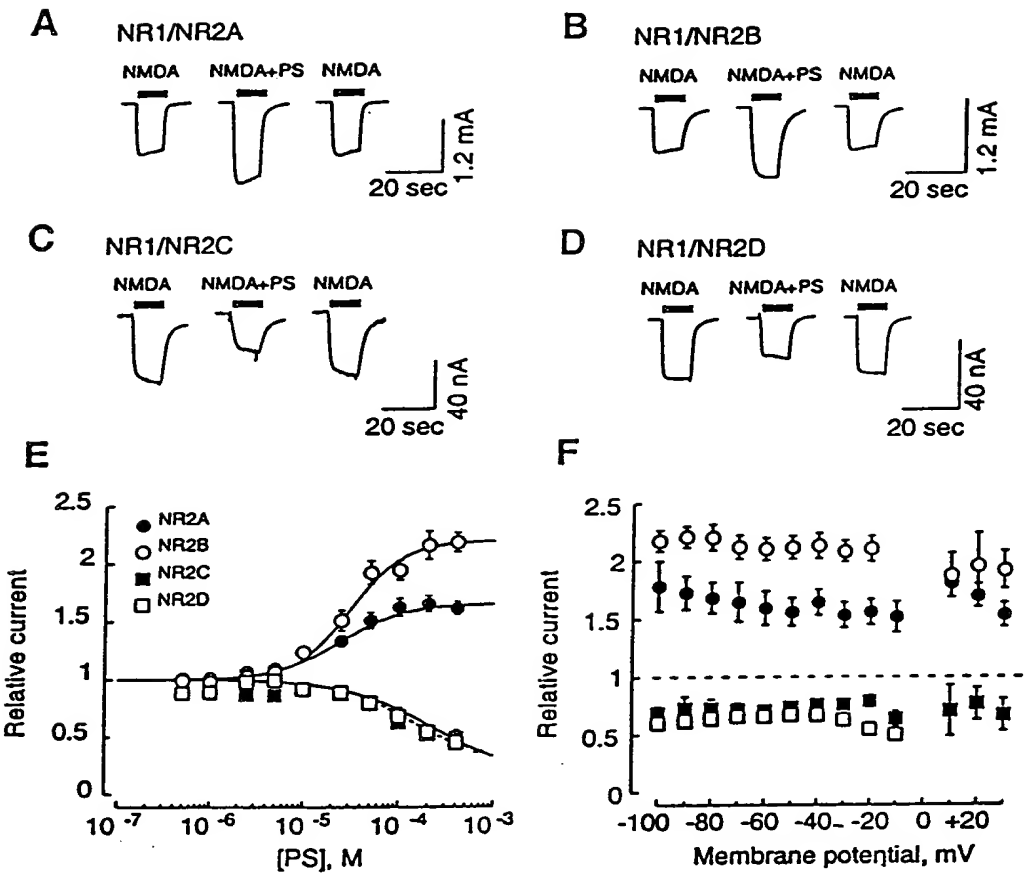

A
NR1/NR2A
NMDA
NMDA+PS
NMDA
1.2 mA
20 sec
B
NR1/NR2B
NMDA
NMDA+PS
NMDA
1.2 mA
20 sec
C
NR1/NR2C
NMDA
NMDA+PS
NMDA
40 nA
20 sec
D
NR1/NR2D
NMDA
NMDA+PS
NMDA
40 nA
20 sec
E
Relative current
NR2A
NR2B
NR2C
NR2D
[PS], M
F
Relative current
Membrane potential, mV

FIG. 26

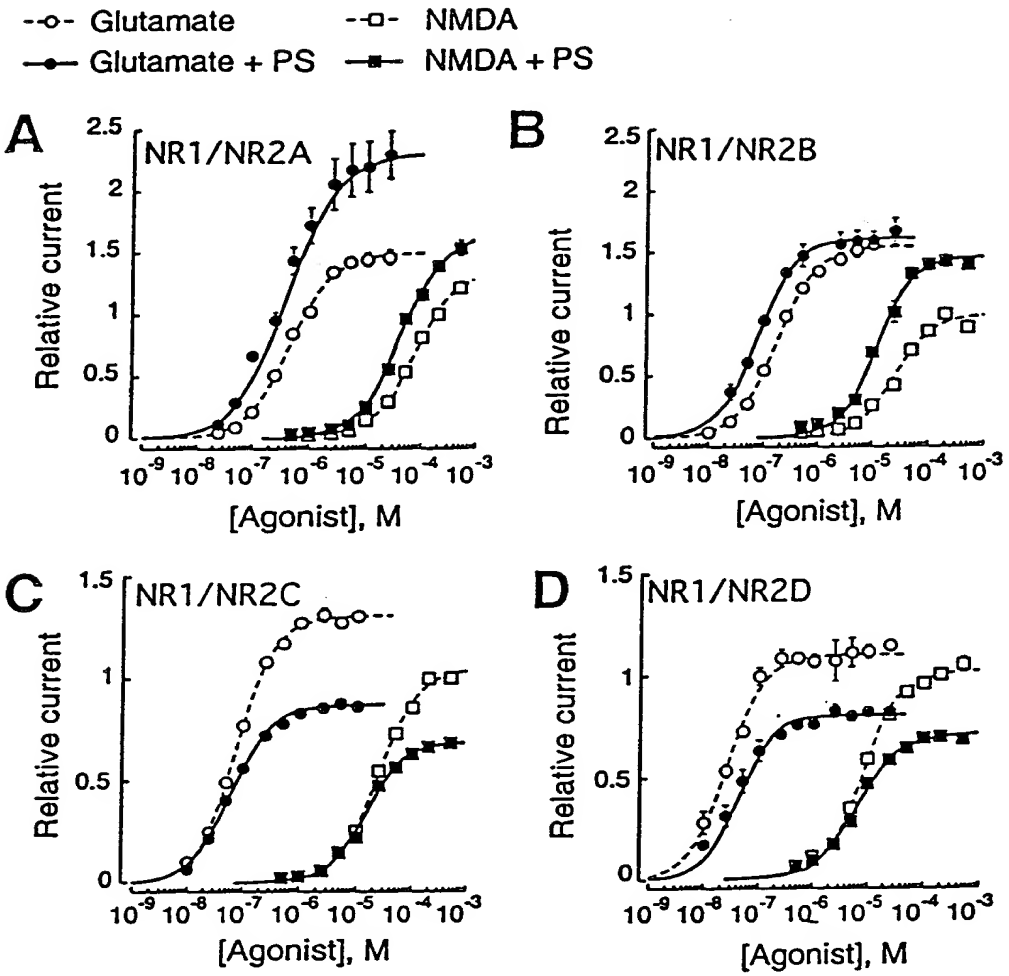

--o- Glutamate
--□- NMDA
—●— Glutamate + PS
—■— NMDA + PS
A
NR1/NR2A
B
NR1/NR2B
C
NR1/NR2C
D
NR1/NR2D
Relative current
[Agonist], M
2.5
2
1.5
1
0.5
0
10-9 10-8 10-7 10-6 10-5 10-4 10-3

FIG. 27

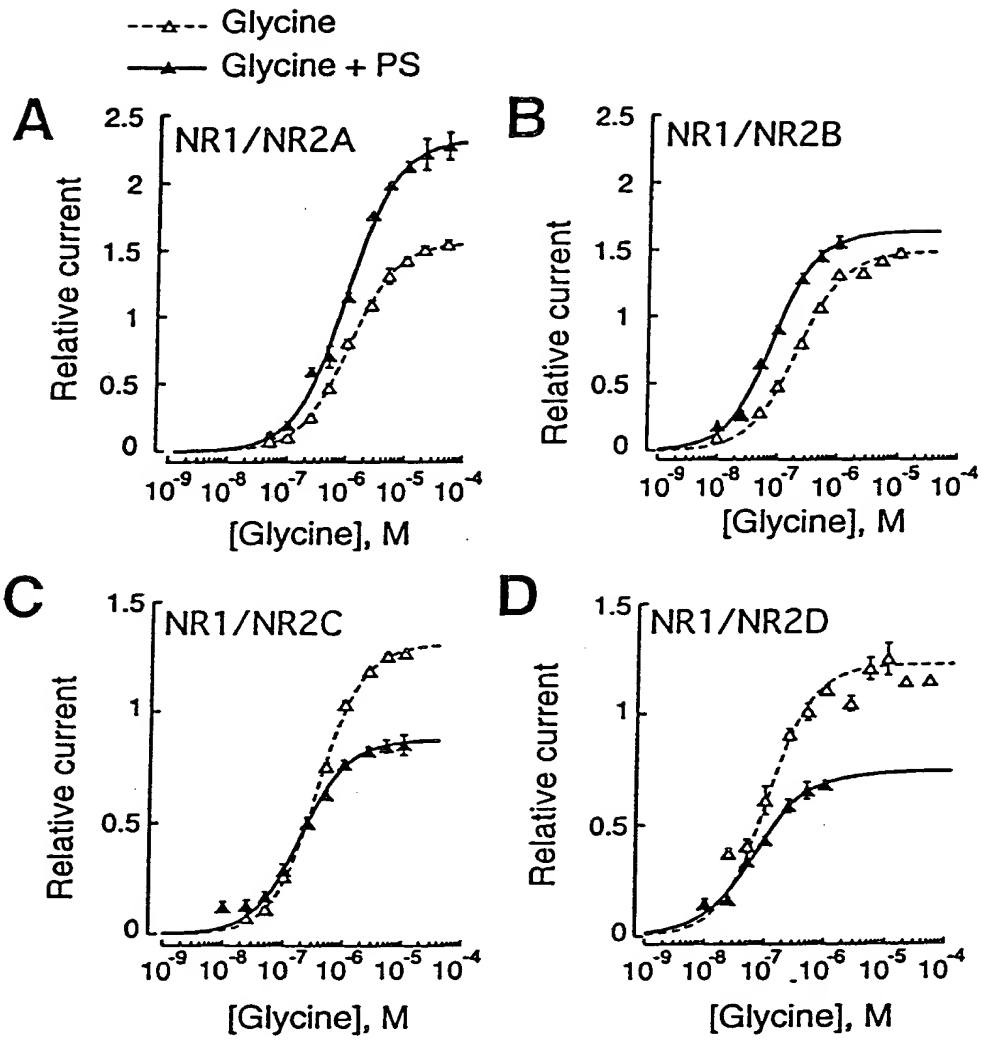

Glycine
Glycine + PS
A
NR1/NR2A
B
NR1/NR2B
C
NR1/NR2C
D
NR1/NR2D
Relative current
[Glycine], M
2.5
2
1.5
1
0.5
0
10^{-9} 10^{-8} 10^{-7} 10^{-6} 10^{-5} 10^{-4}

FIG. 28

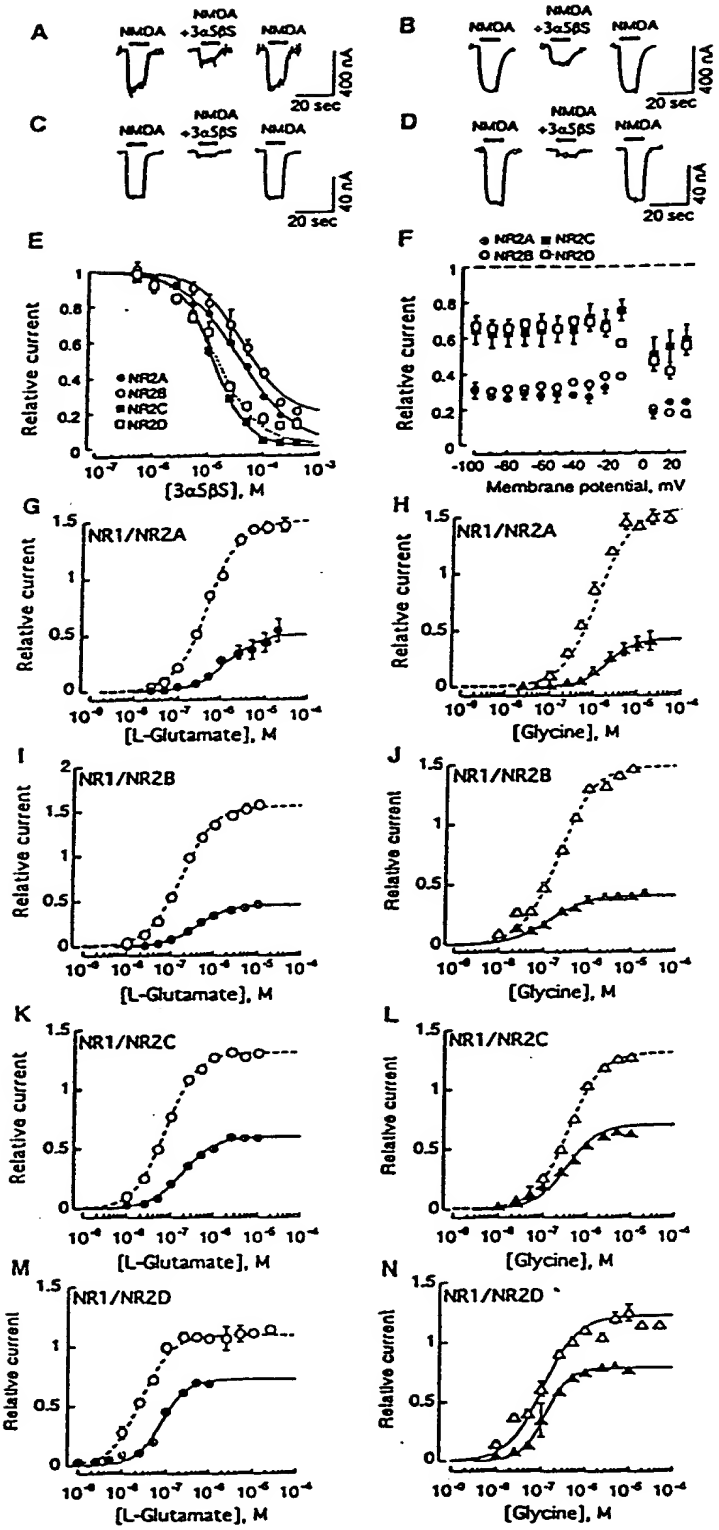

A
NMDA
NMDA +3αSβS
NMDA
400 nA
20 sec
B
C
40 nA
D
E
Relative current
NR2A
NR2B
NR2C
NR2D
[3αSβS], M
F
Membrane potential, mV
G
NR1/NR2A
[L-Glutamate], M
H
[Glycine], M
I
NR1/NR2B
J
K
NR1/NR2C
L
M
NR1/NR2D
N

FIG. 29

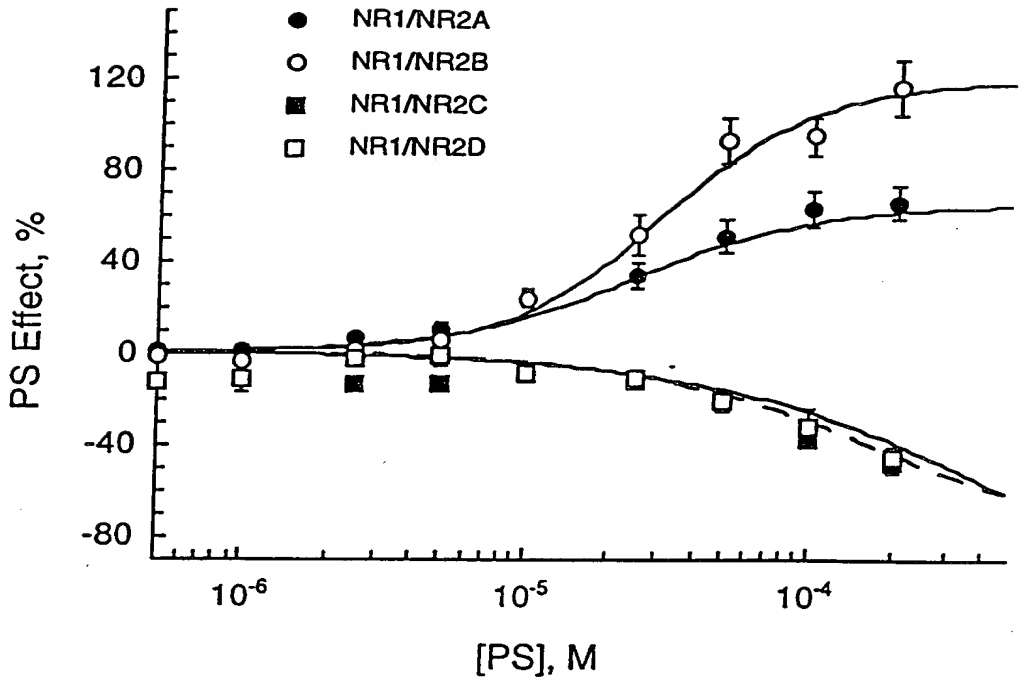


FIG. 30

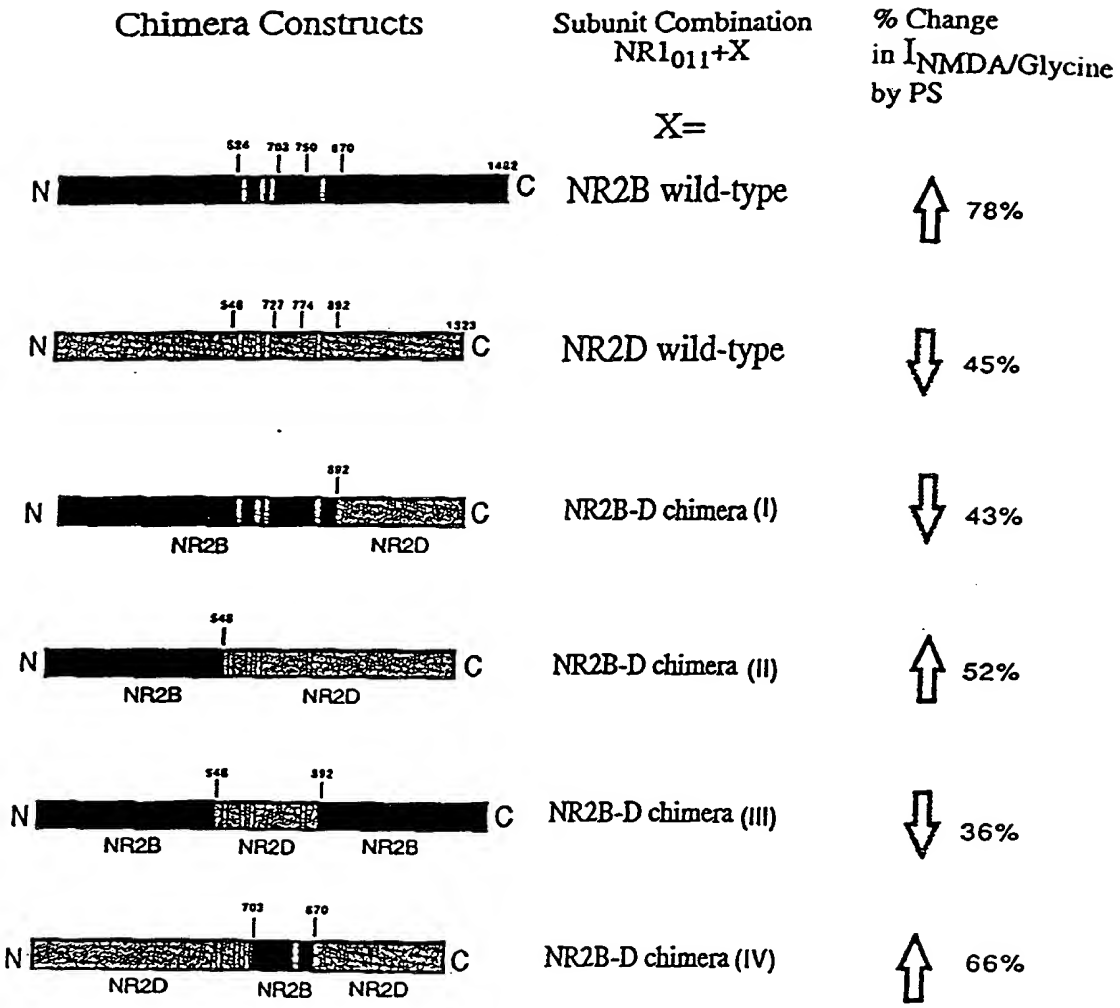

Chimera Constructs
Subunit Combination
NR1011+X
X=
% Change
in INMDA/Glycine
by PS
N
C
NR2B wild-type
78%
NR2D wild-type
45%
NR2B
NR2D
NR2B-D chimera (I)
43%
NR2B-D chimera (II)
52%
NR2B-D chimera (III)
36%
NR2B-D chimera (IV)
66%

FIG. 31

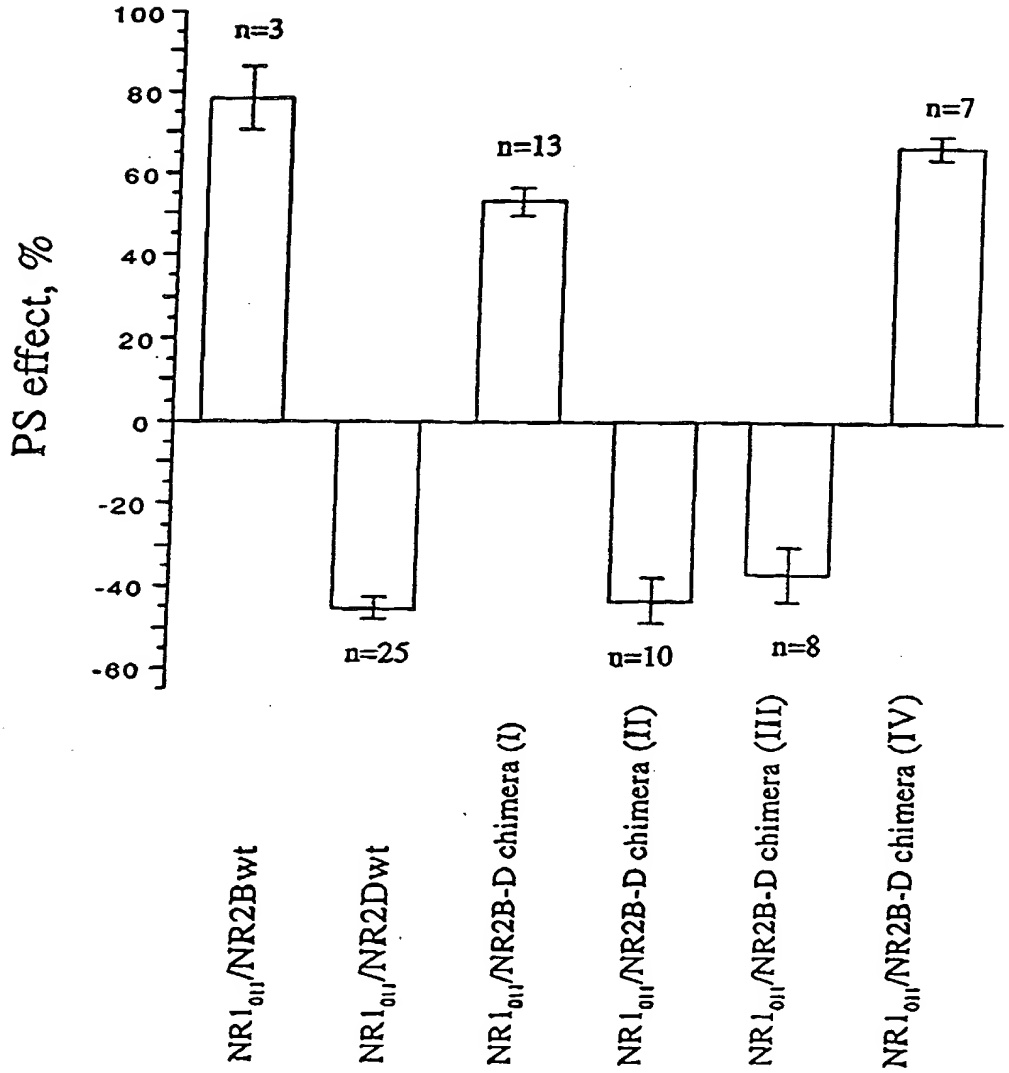

PS effect, %
100
80
60
40
20
0
-20
-40
-60
n=3
n=25
n=13
n=10
n=8
n=7
NR1011/NR2Bwt
NR1011/NR2Dwt
NR1011/NR2B-D chimera (I)
NR1011/NR2B-D chimera (II)
NR1011/NR2B-D chimera (III)
NR1011/NR2B-D chimera (IV)

FIG. 32